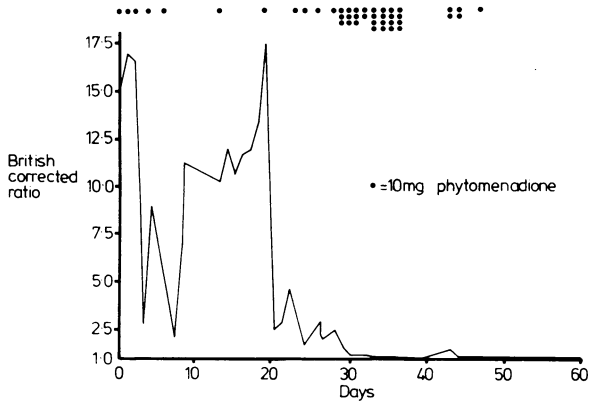
SHORT REPORTS

Difenacoum (Neosorexa) poisoning

Difenacoum is a coumarin anticoagulant developed as a rodenticide[1] that is freely available from supermarkets, chemists, and hardware stores. Accidental or criminal poisoning or self-poisoning is a hazard, and the effect on the anticoagulant mechanism is considerably more prolonged than that of warfarin. The following case history and details of animal experiments indicate the danger associated with this and related compounds.

Case report

A 17-year-old girl had made several suicide attempts since 1978, mostly by drug overdoses. On 7 May 1981 she was admitted having consumed 500 g rat poison (Neosorexa) and swallowed broken razor blades and pins. Coagulation tests gave an initial British corrected ratio of 15·0. Phytomenadione (vitamin K_1; Konakion) was given both by mouth and intravenously at intervals from 7 May to 23 June (figure) before the ingested poison appeared to have been cleared from the system.



Effect of phytomenadione (vitamin K_1) on clotting activity after ingestion of difenacoum.

After a prolonged stay in hospital for psychiatric treatment she was allowed home but required readmission having consumed approximately 1800 g rat bait between 23 November and 6 December together with 40 map pins. She was anaemic (haemoglobin concentration 7·0 g/dl) with a British corrected ratio of 23·0 and required blood transfusion (two units) together with two units of fresh-frozen plasma, which rapidly reduced the British corrected ratio to 5·0. Phytomenadione 10 mg by mouth four times daily resulted in a normal British corrected ratio within 42 days. She subsequently passed 39 pins per rectum; the 40th was removed at gastroscopy.

Animal experiments

The duration of action of difenacoum and its ability to antagonise vitamin K_1 in vivo were investigated in male New Zealand White rabbits (2·5-3·0 kg); measurement of clotting activity and drug administration were as previously described.[2] In the first experiment prothrombin complex activity was measured at intervals after a single dose of difenacoum (0·85 mg/kg). For the first 21 days vitamin K_1 (2 mg/kg) was administered intraperitoneally every two days to prevent death from haemorrhage; during this period prothrombin complex activity was determined immediately before administration of the vitamin.

In the second experiment the effect of a single intravenous injection of vitamin K_1 (0·5 mg/kg) on clotting activity in rabbits anticoagulated (prothrombin complex activity $< 30\%$) with either warfarin 63 mg/kg or difenacoum (0·85 mg/kg) was determined.

Comment

Coumarin anticoagulants such as warfarin are thought to interfere with synthesis of clotting factor by inhibiting the regeneration of vitamin K_1 from its biologically inactive metabolite vitamin K_1 2,3-epoxide.[3] Warfarin and difenacoum produce an accumulation of tritium-labelled vitamin K_1 2,3-epoxide in rabbits after administration of tritium-labelled vitamin K_1,[2] which is consistent with this hypothesis. The duration of anticoagulation produced by difenacoum in the rabbit, however, is much longer than that produced by warfarin.[2,4] Prothrombin complex activity below 50% was recorded 45 days after a single dose of difenacoum (0·85 mg/kg). Furthermore, difenacoum is a more effective antagonist of vitamin K_1 than warfarin in the rabbit. Thus 18 hours after administration of vitamin K_1 prothrombin complex activity was significantly lower ($p < 0{\cdot}001$) in animals pretreated with 0·85 mg difenacoum/kg than in animals pretreated with 63 mg warfarin/kg ($11 \pm 2\%$ *v* $50 \pm 3\%$) even though warfarin was administered in a dose 100 times greater on a molar basis.

The clinical effect of ingestion of difenacoum in man is similar to that observed in animal experiments. These findings indicate that difenacoum is a much more persistent and potent antagonist of vitamin K_1 than warfarin. In cases of poisoning with rodenticides containing difenacoum, which are freely available to the general public, vitamin K_1 should be administered at frequent intervals until the British corrected ratio returns to normal. Thereafter, we suggest that the ratio should be monitored for several weeks to ensure that the pharmacological effect of the drug has stopped.

1 Hadler MR, Shadbolt RS. Novel 4-hydroxycoumarin anticoagulants active against resistant rats. *Nature* 1975;**253**:275-6.

2 Park BK, Leck JB, Wilson AC, Serlin MJ, Breckenridge AM. A study of the effect of anticoagulants on (^{3}H) vitamin K metabolism and prothrombin complex activity in the rabbit. *Biochem Pharmacol* 1979;**28**: 1323-9.

3 Bell RG. Metabolism of vitamin K and prothrombin synthesis; anticoagulants and the vitamin K-epoxide cycle. *Fed Proc* 1978;**37**:2599-604.

4 Park BK, Leck JB, Breckenridge AM. The dose dependent effect of warfarin on vitamin K_1 metabolism and clotting factor synthesis in the rabbit. *Biochem Pharmacol* 1980;**29**:1601-2.

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Treatment of vitamin D_2 poisoning by induction of hepatic enzymes

Drugs that induce synthesis of hepatic microsomal enzymes may, by interference with vitamin D metabolism in the liver, produce hypocalcaemia and osteomalacia.[1] Glutethimide is such a compound,[1] and we used it to treat a patient with vitamin D_2 poisoning who exhibited persistent hypercalcaemia since we thought that its administration would deplete the excess vitamin D from the body stores at a quicker than natural rate, thereby shortening the duration of toxic effects. We report the case here.

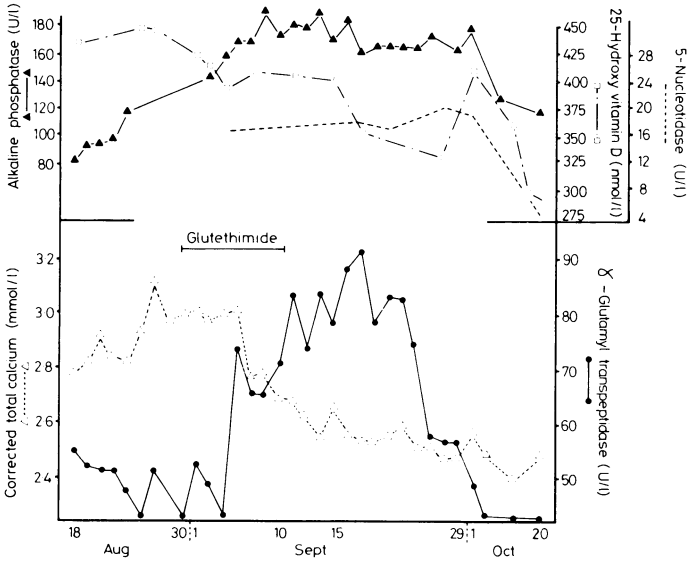
Case report

A 77-year-old woman was admitted as an emergency in a confused state. A clear history was unobtainable. On examination she was obese; no other abnormal findings were noted. Investigations showed calcium concentration 3·52 mmol/l (14·1 mg/100 ml) (normal 2·20-2·70 mmol/l; 8·8-10·8 mg/100 ml); phosphate 0·97 mmol/l (3·0 mg/100 ml) (normal 0·80-1·40 mmol/l; 2·5-4·3 mg/100 ml); alkaline phosphatase 128 U/l (normal 35-130); albumin 41 g/l (normal 30-50); globulin 37 g/l (normal 23-35); total bilirubin 7 μmol/l (409 μg/100 ml) (normal 2-17 μmol/l; 117-994 μg/100 ml); creatinine 229 μmol/l (2·6 mg/100 ml) (normal 40-110 μmol/l; 0·5-1·2 mg/100 ml); alanine aminotransferase 23 U/l (normal 7-45); γ-glutamyl transferase 44 U/l (normal 0-65); IgG 10·0 g/l (normal 5·0-16); IgA 3·34 g/l (normal 0·5-

4·0); and IgM 1·58 g/l (normal 0·5-1·9). No monoclonal Ig was detected in serum by immunoelectrophoresis. A chest x-ray film showed a small discrete mass in the left mid-zone, which was reported as almost certainly a benign lesion.

Prednisolone (15 mg thrice daily) was started, and the serum calcium concentration fell but remained above our reference range. After 10 days the prednisolone was gradually stopped but her serum calcium concentration rose further. It was then discovered that she had been taking vitamin D_2 1·25 mg (50 000 IU) thrice daily for three and a half months before admission. Glutethimide 500 mg at night was started.

Eight days later serum γ-glutamyl transpeptidase activity (a marker of hepatic enzyme induction) rose. The serum calcium concentration fell to within our reference range four days later. Thereafter her confusion and renal function improved considerably. Throughout the period of monitoring there was no biochemical evidence of hepatocellular damage. The figure shows that the raised 25-hydroxy vitamin D concentration fell with enzyme induction but rose again when induction stopped, as indicated by a fall in γ-glutamyl transpeptidase activity, before gradually falling further. There was a significant negative correlation between the corrected serum calcium concentration and γ-glutamyl transferase activity from 10 days before to 10 days after treatment with glutethimide (rank correlation coefficient −0·72; $p < 0·001$).



Serum concentrations of corrected total calcium and 25-hydroxy vitamin D and activities of alkaline phosphatase, 5-nucleotidase, and γ-glutamyl transpeptidase before, during, and after 12 days of glutethimide treatment. (Normal ranges: 5-nucleotidase 5-15 U/l; 25-hydroxy vitamin D 7·5-75 nmol/l.)

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml. 25-Hydroxy vitamin D: 1 nmol/l ≈ 0·4 ng/ml.

Comment

Excessive intake of vitamin D_2 may produce an acute illness, while a lower but supplemental intake may be associated with renal calculi.[2] Hypercalcaemia has been reported to persist up to 14 months after vitamin D_2 has been stopped.[3] We suggest that if poisoning has occurred with heavy doses removal of the excess vitamin may be achieved by induction of hepatic microsomal enzymes. The mechanism remains unknown, but rapid metabolism of vitamin D_2 by hydroxylating enzymes has been suggested.[1] Whether overdosage with the more potent metabolites of vitamin D available therapeutically—namely, alfa-calcidol (1α-hydroxy vitamin D_3) and calcitriol (1α,25-dihydroxy cholecalciferol)—could be successfully treated using this method remains uncertain but merits investigation.

As found in a previous study using inducing agents,[4] the rise in γ-glutamyl transpeptidase activity occurred over about one week. Presumably it takes this time for full alterations in vitamin D metabolism to occur, and therefore enzyme induction would be a useful adjunct to other, more immediate treatment for controlling the acute symptoms of hypercalcaemia from vitamin D poisoning. The rise in plasma alkaline phosphatase and 5-nucleotidase activities is consistent with data suggesting that hepatic membrane-bound enzymes may also be inducible.[1]

The principle of using hepatic-enzyme-inducing drugs is well known in the management of disturbances of bilirubin metabolism.[1] Our patient was treated using the same principle, but clearly more case studies are needed to assess the benefits of glutethimide in vitamin D poisoning. It may be worth considering this form of treatment for intoxication with other exogenous or endogenous fat-soluble compounds that are difficult to excrete, such as vitamin A.

We thank Professor G L Mills, department of geriatric medicine, Royal Liverpool Hospital, for allowing us to report this case, and the SAS Centre Middlesex Hospital for the retrospective estimation of serum 25-hydroxy vitamin D concentrations.

Requests for reprints should be sent to Dr S J Iqbal.

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[2] Taylor WH. Renal calculi and self-medication with multivitamin preparations containing vitamin D. *Clin Sci* 1972;**42**:515-22.
[3] Howard JE, Meyer RJ. Intoxication with vitamin D. *J Clin Endocrinol* 1948;**8**:895-910.
[4] Whitfield JB, Moss DW, Neale G, Orme M, Breckenridge A. Changes in plasma γ-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *Br Med J* 1973;i:316-8.

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Childhood drownings in private swimming pools: an avoidable cause of death

Details were obtained on the circumstances in which children were drowned in private swimming pools during 1975-9. An unknown number of children also suffered severe brain damage as a result of near drowning. The main contributory factor in such accidents is the absence of adequate fencing around pools. Legislation requiring such safety measures to be provided exists in many countries and should be introduced here.

Study and results

Since 1975 the Home Office has collected information from police forces on cases of drowning; it kindly supplied us with information on children drowned in private pools during 1975-9. In this period 34 children (21 boys and 13 girls) were recorded as having been drowned in private pools. All were under the age of 7 years with an average of 2·7 years. Twenty-four were drowned at home and 10 elsewhere; of those drowned elsewhere, five, all boys, were trespassing at the time of the accident. Four of the drownings occurred during or shortly after swimming parties at which adults were present. Rainwater accumulating in pools that had been emptied for the winter caused five deaths. In only three cases was there any fencing around the pools; the victims had entered the area through gates that had been left open.

Serious morbidity may be caused by near drowning. We recently saw two boys, both aged 2½ years, who had been rescued from private swimming pools. Despite resuscitation and treatment in intensive care units they had severe brain damage and both required permanent hospital care.

Comment

Drowning in fresh water is rapid. A 50% chance of death has been calculated for unsupervised children who get into difficulties and lose consciousness in fresh water.[1] There is considerable morbidity among survivors of near drowning, and, though the long-term neurological outlook among children who survive may be surprisingly good, brain damage occurred in 20% in one series[2] of all near drownings in children. Surveys in Australia and Sweden of drownings in private swimming pools showed that the absence of adequate fencing was the main contributory factor, and it has been claimed that 80% of these deaths might be prevented by the provision of such a safety measure.[3 4] Many countries have legislation that requires owners of domestic pools to ensure that they are adequately fenced. In New South Wales, for example, a 1·5 m fence or wall is required and gates must be self-closing and have a latch that is out of reach of small children. There